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EXAMINER	
COTTON, ABIGAIL MANDA	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 02/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/691,528	WILHELM ET AL.	
	Examiner	Art Unit	
	Abigail M. Cotton	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/6/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 6, 2005 has been entered.

Claims 1-19 are pending in the application, with claims 18-19 being newly added. Accordingly, claims 1-19 are being examined on the merits herein.

Applicant's arguments regarding the rejection of the claims under 35 U.S.C. 103(a) have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 and 16-19 are rejected under 35 U.S.C. 112, second paragraph, for lacking enablement for the full scope of the claims. The specification is enabling for a method of inhibiting urokinase to treat a urokinase associated disorder in a patient in need of such urokinase inhibition, said urokinase associated disorder comprising a malignant tumor, metastases and/or lung foci, by administering the composition as claimed (Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide, the L enantiomer thereof or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier) to inhibit urokinase (urokinase plasminogen activator uPA) in said patient, thereby inhibiting the growth and/or spreading of the malignant tumors, metastases and/or lung foci in said patient. However, the specification does not reasonably provide enablement for inhibiting the growth and/or spreading of **any** malignant tumors, metastases and/or lung foci in general, including those not associated with urokinase inhibition.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set

fourth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

1. The nature of the invention: The instant invention pertains to method of inhibiting growth and/or spreading of any malignant tumors, metastases and/or lung foci, including both those mediated by urokinase inhibition as well as any other tumors, metastases, etc. known or unknown that are not affected by urokinase inhibition.

2. The state of the prior art: The skilled artisan would view cancers, metastasis, tumors or lung foci as a group of maladies (cancers) not treatable with one medicament or therapeutic regimen. Treatment efforts and efforts to cure all tumors (cancers) have produced only isolated identifiable positive results. See *In re Application of Hozumi et al,* 226 USPQ 353. Moreover, it is well known that so far no single chemotherapeutic agent has been found to be useful in the treatment of **all** cancers, or even useful in the treatment of all types of tumors, such as all types of breast tumors, brain tumors, etc. For example, breast cancers and leukemia do not share a common

cause and differ in their methods of treatment, i.e., breast cancers are routinely treated with estrogens, antiestrogens and/or androgens, unlike leukemia which is routinely treated with l-asparaginase, daunorubicin, and purine analogs.

3. The predictability of the art, and the breadth of the claims: Note that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 166 USPQ 198 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Moreover, it is known that repeated therapeutic failures, after promising in-vitro results, suggest to the skilled artisan that claims based on in-vitro data, directed to treating cancer or tumors generally, are highly unpredictable, as taught in Trisha Gura's article in *Science*, November 1997:

"[T]he institute started by pulling together mouse models of three tumors: a leukemia, which affects blood cells; a sarcoma, which arise in bone, muscle, or connective tissue; and carcinoma, the most common cells and includes such major killers as breast, colon, and lung cancers. Initially, many of the agents tested in these models appeared to do well. However, most worked against blood cancers such as leukemia and lymphoma, as opposed to the more common solid tumors. And when tested in human cancer patients, most of these compounds failed to live up to their early promise." (See first page, middle column.)

Based on the known teachings of the cancer treatment such as in Trisha Gura's reference, one of ordinary skill in the art would recognize that the treatment in the instant case, including the treatment of numerous and various tumors and cancers such as all types of tumors, mestases and/or lung foci, with the very same compound, is highly unpredictable.

4. The presence or absence of working examples: the specification provides examples of the *in vitro* inhibition of urokinase (see paragraphs 0016-0121, in particular), the treatment of breast cancer in a rat breast cancer model with BN-472 breast cancer tumor fragments (see paragraph 0129, in particular), and in mice having human breast carcinoma cells MDA-BA-231 (see paragraphs 0141-0143, in particular), and the treatment of pancreatic carcinoma in a rat carcinoma model with pancreatic adenocarcinoma CA20948 (see paragraph 012-0136, in particular.) Thus, the evidence in the examples is not commensurate in **scope** with the claimed invention and does not demonstrate criticality of the range of numerous and various tumors, metastases and/or lung foci in the claimed method.

Further, those unknown or future known tumors must require additional or future research to discover and diagnose. Therefor, the skilled artisan has to exercise **undue experimentation** to practice the instant invention.

Thus, the specification fails to provide sufficient support for the broad method of use of the claimed composition for treating numerous and various tumors, metastases and/or lung foci as recited in the instant claims. As a result, one of ordinary skill in the art would be required to perform an exhaustive search for the embodiments of the tumors, metastases and/or lung foci encompassed by the instant claims that are suitable for the practice of the invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for a search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the *Wands* factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of ordinary skill in the art would have to engage in *undue experimentation* to test tumors, metastases and/or lung foci encompassed by the instant claims, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5, 8-12, 15 and 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over the article entitled "Prevention of Breast Cancer Growth, Invasion and Metastasis by Antiestrogen Tamoxifen Alone or in Combination with Urokinase Inhibitor B-428" by Xing et al, Cancer Research 57, 3585-3593, 1997 (of record) in view of the PENTAPHARM Product Catalog 1998 (of record) or the PENTAPHARM Product Catalog 1997 (as provided by Applicants in the IDS dated December 6, 2005.)

Xing et al. teaches a method of preventing breast cancer growth, invasion and metastasis to lungs and lymph nodes (see page 3585, introduction, and page 3589, first full paragraph, in particular), using a urokinase inhibitor in a pharmaceutically acceptable carrier continuously over the course of two weeks (see page 3586, third paragraph, in particular) and in combination with a cytotoxic substance (tamoxifen) (see page 3585, materials and methods, in particular.) Xing et al. teaches that the uPA/uPAR system plays a key role in tumor invasion and metastasis, and inhibition of cell surface uPA activity is an attractive therapeutic target for controlling cellular

invasiveness in cancer (see page 3585, right hand column, second full paragraph, in particular.)

Thus, Xing et al. teaches providing urokinase inhibitors for the treatment of malignant tumors and metastases, as in claims 1, 18 and 19, including tumors that affect that affect the lymph nodes, as in claim 3, and thus the lymphatic system, as in claim 2, and teaches administering a cytotoxic substance as in claim 5. Xing et al. also teaches treating malignant tumors that are breast tumors, as in claim 8. Regarding claim 9, Xing et al. teaches continuous administration of the urokinase drug, and teaches that the TAM can be administered daily (see page 3586, third full paragraph, in particular.) Furthermore, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the dosage regimen for the composition, according to the guidance provided by Xing et al, to provide the desired treatment. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Regarding claims 10-12, Xing et al. teaches a urokinase inhibitor with a pharmaceutically acceptable carrier and tamoxifen (cytotoxic substance.) Regarding claim 15, Xing et al. teaches a minipump comprising a urokinase inhibitor and separate administration of tamoxifen (see page 3585, third full paragraph, in particular), and thus

teaches a "kit" having separate containers for the urokinase inhibitor and cytotoxic substance.

Xing et al. does not specifically teach providing a urokinase inhibitor that is Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide, the L enantiomer thereof, or a pharmaceutically acceptable salt thereof.

The 1998 PENTAPHARM Product Catalog teaches the hydrochloride salt of Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide. The catalog also describes the compound in the following manner: "Pefabloc® uPA is a low molecular weight synthetic inhibitor for urokinase." It is well known in the pharmaceutical arts that a compound must be in the form of a weak acid in order for it to go into a pharmaceutical carrier solution; therefore, it is evident that PENTAPHARM (a company operating under a descriptive and suggestive name giving the impression of being a pharmaceutical manufacturer) manufactured the hydrochloride salt form prospectively in consideration for its use as a pharmaceutical. The 1997 PENTAPHARM Product Catalog as submitted by Applicants provides the same information for Pefabloc® uPA on page 23 of the catalog.

Therefore, it would have been obvious to one of ordinary skill in the art to provide the urokinase inhibitor compound of PENTAPHARM in the composition and/or method

of treatment of Xing et al, because Xing et al. teaches that a treatment method with urokinase inhibitors decreases tumor volume and metastasis, and PENTAPHARM teaches a compound that acts as a urokinase inhibitor. Thus, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the urokinase inhibitor of PENTAPAHRM in the cancer/tumor and metastasis treatment method and/or composition of Xing et al, with the expectation of providing a suitable treatment for the malignant tumors and metastasis. Accordingly, claims 1-3, 5, 8-12, 15 and 18-19 are obvious over the teachings of the references.

Claim 4 is rejected under 35 U.S.C. as being unpatentable over Xing et al, in view of the PENTAPHARM Product Catalog 1998 or 1997, as applied to claims 1-3, 5, 8-12, 15 and 18-19 above, and further in view of the reference "Cancer Principles and Practice of Oncology," fifth Edition, by DeVita et al. Lippincott Williams and Wilkins 1997 (of record.)

Xing et al. and the PENTAPHARM catalogs are applied as discussed above for claims 1-3, 5, 8-12, 15 and 18-19 above, and teach a treatment for breast cancer and tumors of the lungs and lymph nodes with the composition as claimed. Xing et al. and the PENTAPHARM catalogs do not specifically teach that the lymphnodes are selected form the group consisting of axillary and intraperitoneal lymph nodes.

DeVita et al. teaches that it is well known in the art that carcinomas frequently spread and grow in the lymphatic system (see page 139, first full paragraph) and that the ultimate event that leads to mortality in breast cancer is metastasis (see page 1549 first sentence under Angiogensis and Metastasis, in particular.) DeVita et al. teaches that the axillary lymph nodes are affected by the metastasis (see page 139, paragraph bridging left and right hand columns, in particular.) It is furthermore noted that DeVita et al. teach that investigations have focused on plasminogen of secreted plasminogen activator urokinase (see page 150, second full paragraph, in particular) and that metastasis of tumors depends on a balance between enzymes and their inhibitors (see page 1550, third full paragraph, in particular.)

Accordingly, it would have been obvious to provide the composition of Xing et al. and the PENTAPHARM catalogs for the treatment of axillary lymph nodes, as in DeVita et al, because Xing et al. and the PENTAPHARM catalogs teach the composition for the treatment of tumors and metastasis involving lymph nodes, such as metastasized breast cancer, in which urokinase is implicated, and DeVita et al. teaches that the axillary lymph nodes are affected in the metastasis of breast cancer, and that uPA is implicated in the metastasis of the cancers. Thus, one of ordinary skill in the art would have found it obvious to treat axillary lymph nodes with the composition with the expectation of providing a suitable treatment for metastasized tumors affecting the axillary lymph nodes. Accordingly, claim 4 is obvious over the references.

Claims 6-7 and 13-14 are rejected under 35 U.S.C. as being unpatentable over Xing et al, in view of the PENTAPHARM Product Catalog 1998 or 1997, as applied to claims 1-3, 5, 8-12, 15 and 18-19 above, and further in view of U.S. Patent No. 5,736,129 to Medenica et al. (of record.)

Xing et al. and the PENTAPHARM catalogs are applied as discussed above for claims 1-3, 5, 8-12, 15 and 18-19 above, and teach a treatment for breast cancer and tumors of the lungs and lymph nodes with the composition as claimed, and including tamoxifen (cytotoxic agent.) Xing et al. and the PENTAPHARM catalogs do not specifically teach providing a cytotoxic agent that is one of the specific agents recited in claims 6-7 and 13-14.

Medenica et al. teaches a method of treating cancer by the use of a multi-chemotherapeutic drug regime (see abstract, in particular) that makes use of cisplatin (see column 16, lines 8-15, in particular), carboplatin (see column 9, lines 65-67, in particular), doxorubicin (see column 8, lines 39-45, in particular), epirubicin (see column 22, line 28, in particular), 5-fluorouracil (see column 17, lines 11-16, in particular) and paclitaxel (see column 10, lines 24-29, in particular.) Medenica et al. teaches that the regimen is suitable for treating various types of tumors and their metastases (see abstract, in particular), including breast cancer and other types of metastasized cancers (see Experiments 8 and 9, in particular.)

Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to combine the agents of Medenica et al. with the treatment method of Xing et al. and the PENTAPHARM catalogs, because both are directed to the treatment of tumors and their metastases, such as breast cancer tumors and metastases. Note it is considered that "[I]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980.)

Claims 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xing et al, in view of the PENTAPHARM Product Catalog 1998 or 1997, as applied to claims 1-3, 5, 8-12, 15 and 18-19 above, and further in view of U.S. Patent No. 5,449,663 to Haim I. Bicher, issued September 12, 1995.

Xing et al. and the PENTAPHARM catalogs are applied as discussed above for claims 1-3, 5, 8-12, 15 and 18-19 above, and teach a treatment for breast cancer and tumors of the lungs and lymph nodes with the composition as claimed, and including tamoxifen (cytotoxic agent.) Xing et al. also teaches providing tamoxifen, which is a cytotoxic agent, as recited in claim 17. Xing et al. and the PENTAPHARM catalogs do not specifically teach surgically removing the primary tumor from the patient.

Bicher teaches that surgery is one of the major approaches to the treatment of cancer (see column 2, lines 10-30, in particular), and can be combined with chemotherapeutic treatment (see column 2, line 65 through column 3, line 20, in particular.)

Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to surgically remove the tumor, according to the teachings of Bicher, in combination with providing the chemotherapeutic composition of Xing et al. and the PENTAPAHRM catalogs, because the Xing et al. and PENTAPHARM teach the treatment of tumors and metastases, and Bicher teaches that surgery is a primary means of treating tumors. Thus, one of ordinary skill would have found it obvious to perform surgery in combination with the method of the Xing et al. and PENTAPHARM, with the expectation of providing a suitable treatment for malignant tumors.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 10 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 3 of U.S. Patent No. 6,680,320 to Wilhelm et al. The conflicting claims are not patentably distinct from each other because the instant claim recites a pharmaceutical composition comprising the compound as claimed with an additional pharmacologically active substance, whereas the patented claim recited a pharmaceutical composition with a carrier and a second anti-tumor agent. Thus, as an anti-tumor agent is a pharmacologically active substance, as recited in the instant claim, the claims are not patentably distinct.

Claims 11-15 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 3 of U.S. Patent No. 6,680,320 to Wilhelm et al. in view of the teachings of U.S. Patent No. 5,736,129 to Medenica et al, issued Aril 7, 1998. The conflicting claims are not patentably distinct from each other because the instant claims recite a pharmaceutical composition or a kit having the composition comprising the compound as claimed with a cytotoxic substance or radio label, whereas the patented claim recited a pharmaceutical composition with a carrier and a second anti-tumor agent. Medenica et al. teaches the cytotoxic substances as

recited in claims 13-14 for the treatment of tumors, as discussed above. Thus, one of ordinary skill in the art would find it obvious to combine the cytotoxic agents of Medenica et al. into the patented claimed composition, thereby forming the instantly claimed composition. Accordingly, the claims are not patentably distinct from one another.

Claims 1, 8, 18 and 19 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8-9 of U.S. Patent No. 6,624,169 to Wilhelm et al, issued September 23, 2003. The conflicting claims are not patentably distinct from each other because the instant claim recites a method of treating malignant tumors, metastases and/or lung foci with the compound as claimed, whereas the patented claim recites a method of controlling tumors and metastasis by administering a compound having a formula that encompasses the claimed compound. Thus, the instant methods as recited in claims 1, 8 and 18-19 are obvious over the patented claims.

Response to Arguments

Applicant's arguments filed December 6, 2006 have been fully considered but they are not persuasive.

In particular, Applicants argue that the PENTAPHARM catalog reference teaches that the compound inhibits urokinase in *in vitro* tests, but does not teach that the compound inhibits urokinase *in vivo*, or that it is suitable for pharmaceutical and therapeutical applications. The Examiner notes that the PENTAPHARM catalog do not specify whether the urokinase inhibition was determined via *in vitro* or *in vivo* tests. Nonetheless, the Examiner respectfully notes that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Xing et al. teaches the desirability of providing urokinase inhibitor for the treatment of tumors, whereas the PENTAPHARM catalogs teach that the compound as claims acts as a urokinase inhibitor. Accordingly, it would be obvious to incorporate the urokinase inhibitor compound of the PENTAPHARM catalog into the method of Xing et al. with the expectation of reducing tumor growth.

Applicants further argue that Xing et al. cannot be considered as teaching the general use of urokinase inhibitor as antitumor agents alone or in combination with other active substances, as Xing et al. only provides data for a single urokinase inhibitor (B-428.) The Examiner respectfully disagrees because while Xing et al. focuses on B-428 to provide experimental *in vivo* and *in vitro* data, Xing et al. also provides motivation for the treatment of malignant tumors and metastases with urokinase inhibitors in general by teaching that, for example, uPA/uPAR system plays a key role in tumor

invasion and metastasis, and inhibition of cell surface uPA activity is an attractive therapeutic target for controlling cellular invasiveness in cancer (see page 3585, right hand column, second full paragraph, in particular), and teaches specifically providing a synthetic inhibitor of uPA (B-428) to inhibit tumor cell growth (see abstract, in particular.) Accordingly, it is considered that the Xing et al. reference provides the motivation for treatment of tumors and metastasis where uPA is implicated with urokinase inhibitors.

Applicants further assert that the *in* vitro inhibition of urokinase does not correlate well with the *in vivo* inhibition of urokinase, and cite references by Rockway and Giranda, Pilat et al, and Steinmetzer. Regarding the Rockway and Giranda reference, Applicants argue that the reference shows that it is known in the art that most of the known urokinase inhibitors are not suitable to enter preclinical trials and thus are not pharmacologically useful. However, the Examiner notes that while this reference indicates the unsuitability of some newly developed uPA inhibitors for pharmacological use, the article nonetheless is directed to **the search for synthetic UPA inhibitors** that may be used in the treatment of conditions such as tumors (see page 1483, in particular.) Rockway and Giranda teach that certain uPA inhibitors have been shown to slow the growth or spread of tumors (see page 1484, fourth full paragraph, in particular), although certain uPA inhibitors such as amiloride have given mixed results in the treatment of tumors. Rockway and Giranda specifically teach that a school of thought regarding uPA inhibitors is the improved uPA inhibitors will provide better tumor treatment results. Thus, Rockway and Giranda do not teach that compounds exhibiting

in vitro urokinase inhibition are unlikely to be pharmacologically useful, as asserted by Applicants, and instead teach that urokinase inhibitors are a likely and desirable target for tumor therapies.

Applicants argue that the Pilat reference teaches that amiloride (a type of urokinase inhibitor) was ineffective as an antitumor agent. The Examiner respectfully disagrees with this assertion. Pilat teaches that amiloride did not inhibit tumor growth or metastases development in a model of rat prostate cancer. However, Pilat et al. further teaches that amiloride has been shown to inhibit tumor growth and metastasis in several other tumor systems (see abstract, in particular.) Thus, Pilat et al. does not teach that amiloride is ineffective as an antitumor agent in general, and instead teaches that amiloride is not effective in the treatment of a specific type of cancer, prostate cancer. The Examiner further notes that Pilat et al. abstract as provided by Applicants does not mention the urokinase inhibiting activity of amiloride, or address the activity of urokinase in the tested cancers. Thus, Pilat et al. does not teach away from providing urokinase inhibitors in the treatment of tumors and/or metastases.

Applicant's further argue that the Steinmetzer reference teaches compounds having *in vitro* antimetastatic ability that were poorly soluble and thus not pharmacologically useful. However, the Examiner notes that, as in the Rockway and Giranda reference, the Steinmetzer reference as a whole is directed to the search for urokinase inhibitors as potential antitumor drugs (see title in particular.) Thus, rather

than teaching that compounds having urokinase inhibiting activity (in vitro or in vivo) are not suitable for the treatment of tumors, this reference teaches the desirability of such compounds as potential antitumor agents. Thus, one of ordinary skill in the art would understand from the teachings of Steinmetzer that while certain urokinase inhibitors may not be suitable for pharmacological use, for example because of poor solubility, in general such inhibitors are highly desirable for potential tumor treatments.

Applicants further argue that none of the references disclose the particular claimed urokinase inhibitor in combination with the specific cytotoxic antitumor agents as claimed. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In particular, it is noted that the Medenica et al. reference teaches the cytotoxic agents as claimed, as has been discussed above.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abigail M. Cotton whose telephone number is (571) 272-8779. The examiner can normally be reached on 9:30-6:00, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AMC

SHENGJUN WANG
PRIMARY EXAMINER